PATENT COOPERA

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

To:
NOVARTIS AG
Corporate Intellectual Property
Attn. Lehmeier, Thomas J.
CH-4002 Basel
SWITZERLAND

Applicant's or agent's file reference DV/4 -33696A	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/EP2005/003062	International filing date *(day/month/year)* 22/03/2005
Applicant NOVARTIS AG	

Date of mailing *(day/month/year)* 26/06/2006

1. [x] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41-22) 338.82.70

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the International application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until **30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Jens Ambrosch

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims,description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
DV/4 -33696A		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP2005/003062	22/03/2005	23/03/2004
Applicant		
NOVARTIS AG		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
      [ ] The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box II).

3. [ ] **Unity of invention is lacking** (see Box III).

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant.
      [ ] as selected by this Authority, because the applicant failed to suggest a figure.
      [ ] as selected by this Authority, because this figure better characterizes the invention.
   b. [X] none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/003062

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, MEDLINE, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 768 114 A (BOEHRINGER INGELHEIM PHARMACEUTICALS INC) 16 April 1997 (1997-04-16) page 3, line 35 - line 54 page 4, line 35 - page 5, line 22 page 6, line 20 - line 22 page 9, line 54 - page 10, line 46; examples 5-8 claims 1-27	1-22
X	US 6 228 346 B1 (ZHANG ZHENGFENG ET AL) 8 May 2001 (2001-05-08) column 3, line 23 - line 35 column 5, line 5 - line 20 column 7, line 36 - column 8, line 33 column 8 - column 9; examples 1,2	1-22

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 June 2006	26/06/2006

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Muller, S

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Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/65469 A (RTP PHARMA INC) 23 December 1999 (1999-12-23) page 7, line 12 - line 17 page 12 - page 13; example 4 claims 1-3	1-22
X	EP 0 726 088 A (GRÜNENTHAL GMBH) 14 August 1996 (1996-08-14) column 6; example 1 claims 1-7	22

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2005/003062

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0768114 A	16-04-1997	CA 2187698 A1	14-04-1997
		JP 9122466 A	13-05-1997
US 6228346 B1	08-05-2001	AT 264673 T	15-05-2004
		AU 2888397 A	19-11-1997
		DE 19616573 A1	06-11-1997
		WO 9740824 A2	06-11-1997
		EP 0909168 A2	21-04-1999
WO 9965469 A	23-12-1999	AT 233549 T	15-03-2003
		AU 755993 B2	02-01-2003
		AU 4693899 A	05-01-2000
		CA 2335472 A1	23-12-1999
		CN 1312708 A	12-09-2001
		DE 69905716 D1	10-04-2003
		DE 69905716 T2	05-02-2004
		EP 1089714 A2	11-04-2001
		ES 2194477 T3	16-11-2003
		JP 2002518318 T	25-06-2002
		SE 521255 C2	14-10-2003
		SE 0004620 A	08-02-2001
EP 0726088 A	14-08-1996	AT 243070 T	15-07-2003
		BR 9600488 A	03-03-1998
		DE 69628685 D1	24-07-2003

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/003062	22.03.2005	23.03.2004

International Patent Classification (IPC) or both national classification and IPC
INV. A61K9/14

Applicant
NOVARTIS AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	see form PCT/ISA/210	Muller, S Telephone No. +31 70 340-2080

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	7,15,21,22
	No:	Claims	1-6,8-14,16-20
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-22
Industrial applicability (IA)	Yes:	Claims	1-22
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. Cited Documents

The following documents are referred to in this communication:

D1: EP-A-0 768 114 (BOEHRINGER INGELHEIM PHARMACEUTICALS INC) 16 April 1997 (1997-04-16)

D2: US-B1-6 228 346 (ZHANG ZHENGFENG ET AL) 8 May 2001 (2001-05-08)

D3: WO 99/65469 A (RTP PHARMA INC) 23 December 1999 (1999-12-23)

D4: EP-A-0 726 088 (GRÜNENTHAL GMBH) 14 August 1996 (1996-08-14)

2. Novelty

D1 discloses (see page 4, line 35 - page 5, line 22 and examples 5-8 on pages 9,10) a method for homogenization and micronization of a pharmaceutically active ingredient such as ipratropium bromide and albuterol sulfate comprising subjecting a suspension of the active ingredient in a propellant by high pressure homogenization. The subject-matter of claims 1,2,5,6,9-14,16-18,20 is therefore not new (Article 33(2) PCT)

D2 discloses (see examples 1 and 2 on columns 8 and 9) pharmaceutical aerosols for micronizing pharmaceuticals for pulmonary application, which contains a propellant mixture existing in a subcritical state and including two classes of propellant gasses, wherein at least 80% w/w of the micronized pharmaceuticals have a diameter of less than 8 microns. The operating pressure of the composition is preferably for 5 to 20 bar. The subject-matter of claims 1-6,8,11-14,16-20 is therefore not new (Article 33(2) PCT).

D3 discloses (see example 4 on pages 12, 13 and the claims) a process for preparing sub-micron particles of an active compound of up to 2 microns in size comprising: a) dissolving the active compound in a liquefied compressed gas solvent therefor, b) expanding the compressed fluid solution, c) high pressure homogenizing the suspension

from step b), d) recovering the microparticles so produced.The subject-matter of claims 1-6,8,11,12,16-18,21 is therefore not new (Article 33(2) PCT).

3. Inventive Step

Claims 1-6,8-14,16-20 not being new are also not inventive.
Dependent claims 7,15 and 21 are not considered to be inventive since their subject-matter concerns mere process optimisations that the expert in the field would undertake without the involvment of inventive skills (Article 33(3) PCT).

Regarding independent claim 22
D1 is considered as being the closest prior art. It discloses (see claim 25) a apparatus for homogenizing and micronizing (see page 5, lines 6,7) an aerosol formulation in a closed continuous -loop apparatus under elevated pressure, the apparatus comprising:
- a mixing vessel
- means for performing high pressure homogenization and
- means for connecting said reaction vessel and said means for performing high pressure homogenization in a closed continuous-loop apparatus.

Independent claim 22 differs from D1 in that it discloses two stirred pressure vessels instead of one which is used in a closed continuous-loop.
In the present application, the suspension is formed in a first stirred vessel and stored in a second vessel after the micronization process, whereas in D1 the same stirred vessel is used before and after the micronization process.
Using a second stirred vessel for storing the suspension instead of using the same vessel a second time is considered to be an obvious alternative to the skilled person who seeks to micronize an active agent by high pressure homogenization .
Present claim 22 therefore appears not to be inventive over the prior art (Article 33(3) PCT).

4. Industrial applicability

Claims 1-22 satisfy the criterion of industrial applicability set forth in Article 33(4) PCT.